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PATENT APPLICATION
Docket No.: LKS94-04A2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Michael J. Briskin, Douglas J. Ringler, Dominic Picarella and Walter Newman

Application No.: 08/875,849 Group Art Unit: 1644

371(c) Date: September 8, 1997 Examiner: R. Schwadron

Int'l Filing Date: February 12, 1996

For: MUCOSAL VASCULAR ADDRESSINS AND USES THEREOF

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231

on 6/1/99 (Date) B. J. Nannis (Signature)

B.J. Nannis

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REPLY TO RESTRICTION REQUIREMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Responsive to the Restriction Requirement dated March 30, 1999, the claims of Group I (Claims 24 - 32), drawn to fusion proteins comprising primate MAdCAM, are elected, with traverse, for prosecution. Applicant reserves the right to file a continuing application or take such other appropriate action as deemed necessary to protect the inventions of Groups II - VI. Applicant does not hereby abandon or waive any rights in the inventions of Group II - VI.

A one-month extension of time to respond to the Office Action is respectfully requested. A Petition for Extension of Time and the appropriate fee are being filed concurrently.

The Restriction Requirement dated March 30, 1999 is being traversed for the reasons set forth in detail below.

GROUNDS FOR TRAVERSAL

The Examiner stated that the subject application contains multiple inventions (inventions of Groups I - VI) which are not so linked so as to form a general inventive concept under PCT Rule 13.1. According to the Examiner the application contains claims directed to the following inventions:

Group I, Claims 24 - 32, drawn to fusion proteins comprising primate MAdCAM-1;
Group II, Claims 33 and 34, drawn to nucleic acids;
Group III, Claims 37 and 38, drawn to a method of making a fusion protein;
Group IV, Claims 44 and 46, drawn to methods of detection using fusion proteins;
Group V, Claims 89 - 93, drawn to a method of treatment with an antibody; and
Group VI, Claims 94 - 100, drawn to a method of treatment with fusion proteins or primate MAdCAM-1.

The Examiner has required election of a single invention to which the claims must be restricted under 37 C.F.R. § 1.499, stating that the inventions of Groups I - VI do not form a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical feature. In support of his position, the Examiner states that the special technical feature of the claimed inventions is primate MAdCAM-1, and that Butcher *et al.* (WO 94/13312) teaches primate MAdCAM-1 and the use of MAdCAM-1 to treat disease. The Examiner concludes that the technical feature linking the inventions of Groups

I - IV does not constitute a special technical feature as defined by PCT Rule 13.2, because it does not define a contribution over the prior art.

Applicant respectfully disagrees with the Examiner's conclusion. Butcher *et al.* teaches murine MAdCAM-1 and a nucleic acid which encodes the murine protein. Butcher *et al.* also teaches that "the mucosal addressin (i.e., MAdCAM-1) can come from any species" (WO 94/13312, at page 4, line 14) and that a "cDNA of one species can be used to probe cDNA or genomic libraries of another species to identify and isolate the gene from the other species" (WO 94/13312, at page 8, second paragraph). However, the reference does not contain a working example of this process, and does not disclose a MAdCAM-1 or a nucleic acid encoding a MAdCAM-1 of any species other than mouse.

Applicant's attempts to isolate and clone a primate MAdCAM-1 cDNA by low-stringency cross hybridization using the murine MAdCAM-1 cDNA as probe, in accordance with the teachings of Butcher *et al.*, or by the Polymerase Chain Reaction using degenerate primers based upon the sequence of murine MAdCAM-1, were unsuccessful. As evidence of this lack of success, Shyjan *et al.*, a later publication co-authored by inventor Briskin, is provided herewith in the Third Supplemental Information Disclosure Statement being filed concurrently (Reference AX4). Shyjan *et al.* clearly states that:

> Previous studies in our laboratory by both low stringency cross-hybridization to zoo blots and degenerate PCR based on murine MAdCAM-1 sequences, indicated that a human MAdCAM-1 gene sequence was not well conserved. (Shyjan *et al.*, at page 2852, column 1, lines 24-27).

Shyjan *et al.* further states that:

> Initial attempts to clone the human homologue to murine MAdCAM-1 by low stringency cross-hybridization suggested that nucleotide conservation between murine MAdCAM-1 and higher species was poor . . . (Shyjan *et al.*, at page 2853, column 1, lines 3-6).

Further evidence of the difficulty encountered cloning a cDNA encoding primate MAdCAM-1 is that a substantial amount of time elapsed between the initial report of murine MAdCAM-1 in U.S. Serial No. 07/990,866 (filed December 15, 1992, see Butcher *et al.*) and the filing of

Applicant's patent application regarding primate MAdCAM-1 (U.S. Serial No. 08/523,004, filed September 1, 1995).

As described in the subject application, Applicant successfully cloned macaque MAdCAM-1 cDNA only after developing an expression cloning strategy. Later, it was discovered that the sequences of murine and primate (macaque and human) MAdCAM-1 are dramatically divergent at both the nucleotide and amino acid level (Specification, at pages 57 and 58). This divergence likely explains why Applicant's attempts to isolate primate MAdCAM-1 in accordance with the teachings of Butcher *et al.* were unsuccessful.

At best, the teachings of Butcher *et al.* might have lead a person of ordinary skill in the art to attempt to isolate a primate MAdCAM-1 by cross-hybridization with the murine cDNA; however, such an attempt would fail due to the divergent sequences of murine and primate MAdCAM-1. Thus, Butcher *et al.* is not an enabling reference as it does not teach the person of ordinary skill in the art how to successfully isolate a primate MAdCAM-1. Applicant's primate MAdCAM-1 should be considered as a special technical feature under PCT Rule 13.2, as it is both novel and nonobvious over the teachings of Butcher *et al.*, and therefore defines a contribution over the prior art.

Applicant respectfully requests reconsideration of the Restriction Requirement and suggests that the Restriction Requirement be modified by joining the inventions of Group I (fusion proteins), Group IV (method of detection using fusion proteins) and Group VI (method of therapy using fusion proteins or primate MAdCAM-1), and by joining the inventions of Group II (nucleic acids) and Group III (method of using nucleic acids to produce fusion proteins). The proposed modification will result in three groups (i.e., (1) Groups I, IV, and VI; (2) Groups II and III; and (3) Group V), the claims of which each share a special technical feature, namely, (1) fusion proteins, (2) nucleic acids encoding fusion proteins, and (3) antibodies reactive with primate MAdCAM-1, respectively.

The inventions of Groups I - VI, as defined by the Examiner, are believed to be patentably distinct from each other, and the suggestion to combine the claims of Groups I, IV and

should not be construed as an indication that Applicant believes that the patentably distinct claims within the joined groups stand or fall together.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Helen E. Wendler

Helen E. Wendler
Registration No. 37,964
Telephone (781) 861-6240
Facsimile (781) 861-9540

Lexington, Massachusetts 02421-4799

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